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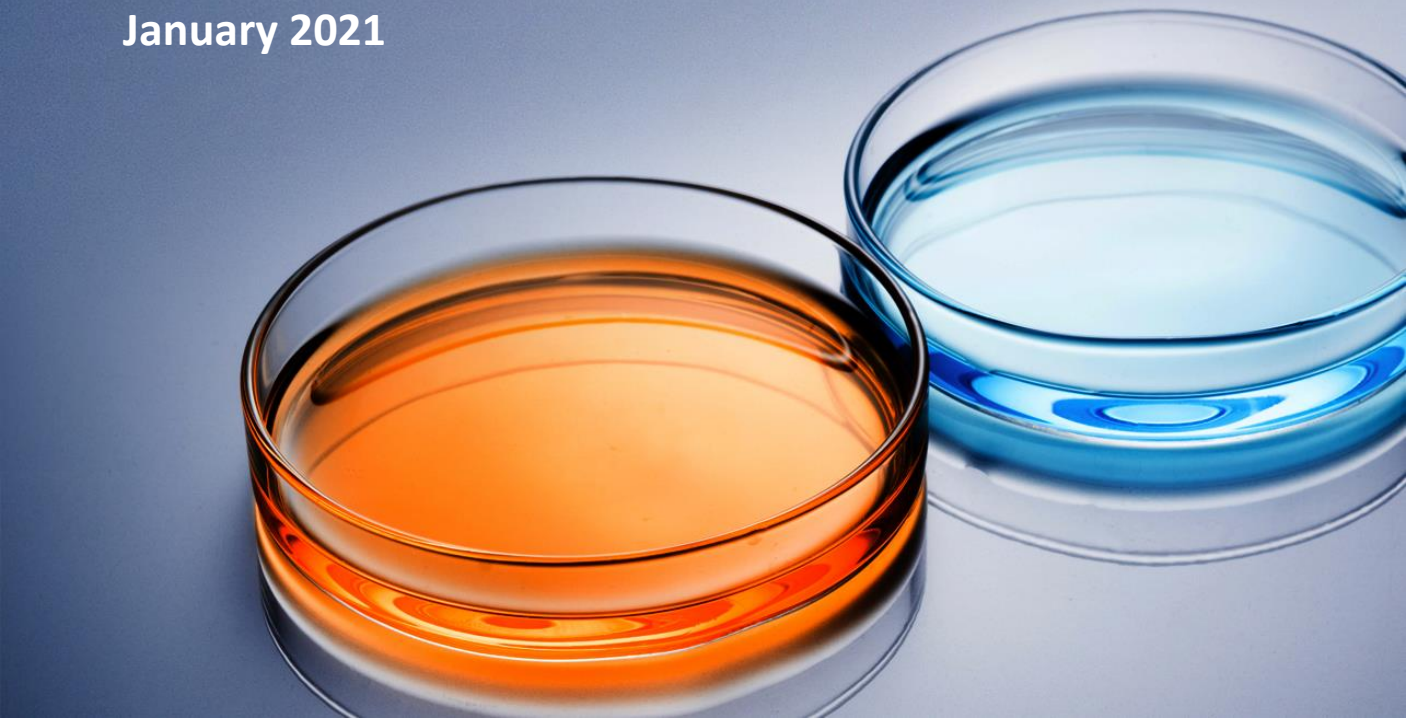
Chlorhexidine Digluconate (7.1%) Gel Job Aid to Assist with Dossier Preparation

January 2021



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The Promoting the Quality of Medicines Plus (PQM+) Program is a five-year cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases, as well as improve maternal, newborn, and child health.

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- Alison Collins, Health Systems Advisor
- Lisa Ludeman, Senior Pharmaceutical Management Advisor
- Tobey Busch, Senior Pharmaceutical Management Advisor
- Helen Petach, Senior MCH Science Advisor, USAID.

Contents

Acronyms

4CA	4-Chloroaniline
API	active pharmaceutical ingredients
CHX	Chlorhexidine
CTD	common technical document
CQA	critical quality attribute
HPLC	high performance liquid chromatography
Ph. Eur.	European Pharmacopeia
PLC	programmable logic controller
PQM+	Promoting the Quality of Medicines Plus
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention

This document is a job aid to enable quick access to technical information by those preparing dossiers for Chlorhexidine (CHX) digluconate (7.1%) gel. The information consists of facilities, equipment, safety recommendations, and analytical data for production. The information herein is adapted from the Promoting Quality Medicines Program's Chlorhexidine digluconate (7.1%) gel Product Information Report (May 2019).

Aid for CTD Module 2.3.A.1 – Facilities and Equipment

Table 1. Facilities for Processing CHX Gel

Parameter	Comments
Permitted Daily Exposure Equipment and Facility Controls	• Consult toxicological information and regulatory authorities.
Compounding CHX Gel	• Vessel – A) suitably sized and jacketed for heating and cooling; B) sealable stainless steel; C) PLC control system, e.g., Siemens PCS7 controller • Variable speed, bidirectional homogenizer • Variable speed agitator • Vacuum and compressed air for material transfer • Stainless steel conical vessels for intermediate bulk storage (200–300 Kg capacity) for CHX gel
CHX Gel Bulk Product Equipment	• Proper geometry for 1) uniform mixing across vessel, e.g., spherical or conical that avoids dead spaces; and 2) good product recovery • Allows vacuum deaeration with controlled addition of liquids and solids • Mixing system for uniform mixing without vortices • External heating and cooling jacket

Aid for CTD Module 3.2.S.1.3 – API Physicochemical Attributes

Table 2. API Physicochemical Properties

Test	Comments
Appearance	• CHX digluconate solution, 20% w/v is a clear to pale yellowish liquid conforming to the European Pharmacopeia (Ph. Eur.) Monograph for description.
Identity and Assay	• Identity and Assay by ultraviolet and high performance liquid chromatography (HPLC) • Identity and Assay by HPLC per Ph. Eur. Monograph for description

pH	• CHX digluconate active pharmaceutical ingredients (API) solution should be controlled within the range of 5.5–7.0 to minimize impurity formation, e.g., 4CA and others.
4CA (most critical impurity)	• Impurity supplier specification ≤ 20 ppm in CHX digluconate solution (20% w/v) • Stays below 150 ppm ≤ 6 months at Zone II (25°C/60% RH) • Should be controlled within the range of 5.5–7.0 • Impacts 4CA and other impurity formation and should be controlled for stability • 4CA formed by pH and thermal stress • 4CA is a CQA – genotoxic and carcinogenic
Other Impurities	• Occur via hydrolysis, condensation, and other mechanisms • Controlled in accordance with the levels permitted in the Ph. Eur. Monograph
Thermal Stability	• Stable for 6 months under Zone II climatic conditions (25°C/60% RH)

Aid for CTD Module 3.2.S.3.2 – Impurities

Table 3. CHX Impurities

CQA Parameter	Release Specification (acceptance criteria)	Shelf-life Specifications (acceptance criteria)
4CA (Impurity P)	NMT 0.08%	NMT 0.35%
1-(6-aminohexyl)-5-(4-chlorophenyl) biguanide (Impurity G)	NMT 0.3%	NMT 0.6%
1-[6-(carbamimidoylaminohexyl] -5-(4chlorophenyl) biguanide (Impurity N)	NMT 1.0%	NMT 2.0%
1-(4-chlorophenyl)-5[6-[[4-[(4-chlorophenyl) amino]-6[(1S,2R,3R,4R)-1,2,3,4,5pentahydroxypentyl]-1,3,5-triazin2-yl] amino] hexyl] biguanide (Impurity J)	NMT 0.4%	NMT 0.7%
1,1-[iminobis(carbonimidoyliminohe xane-6,1diyl) bis [5-(4-chlorophenyl) biguanide] (Impurity H)	NMT 0.5%	NMT 0.5%
1-(4-chlorophenyl)-5[6[cyanocarbamimidoyl)amino] hexyl] biguanide (Impurity A)	NMT 0.4%	NMT 0.4%
Sum of Impurity (I+O), 5-(2-chlorophenyl)-5'(4chlorophenyl)-1&1'-(hexane-1,6diyl) dibiguanide	NMT 0.4%	NMT 0.4%

N-(4-chlorophenyl)-N'[[6[[[(4chlorophenyl) carbamimidoyl] carbamimidoyl] amino] heyxl] carbamimidoyl] urea (Impurity K)	NMT 0.4%	NMT 0.7%
N-(4-chlorophenyl) urea (Impurity F)	NMT 0.2%	NMT 0.3%
Any other specified impurities*	NMT 0.2%	NMT 0.2%
Any other unspecified impurities	NMT 0.1%	NMT 0.2%
Total impurities	NMT 2.0%	NMT 4.0%
Microbial content	Complies with harmonized pharmacopeia	
Total aerobic microbial count	$\leq 10^2$ cfu/g	$\leq 10^2$ cfu/g
Total combined yeasts/mold count	$\leq 10^1$ cfu/g	$\leq 10^1$ cfu/g
Staphylococcus aureus	Absent in 1g	Absent in 1g
Pseudomonas aeruginosa	Absent in 1g	Absent in 1g

** Any other specified impurities include:*

1. *1-[[6-[[[(4-chlorophenyl) carbamimidoyl] carbamimidoyl] amino] hexyl] carbamimidoyl] urea (Impurity B)*
2. *(5R,6S)-2-[(4-chlorophenyl) amino]-5-hydroxy-6-[(1R,2R)-1,2,3-trihydroxypropyl]-5,6-dihydro-4H-1,3-oxazin-4-one (Impurity L)*
3. *Impurity Q*

Table 4. CHX Elemental Impurities

Substance	Specification
Elemental Impurities (per ICH Q3D)	• Risk assessment should be conducted to include: A) input API; B) excipients; C) processing aids (water); D) manufacturing equipment; and E) contain closure systems. The oral route guidance should be used for CHX gel. • Risk assessment focuses on Class 1 (cadmium, lead, arsenic, and mercury); Class 2A (cobalt, vanadium, and nickel) elemental impurities. • Likelihood of reaching final dose should be deemed to be low. • Very low levels of relevant elements, <10% of permitted daily exposure limit, can be approved in final product.

Aid for CTD Module 3.2.P.2.3 – Manufacturing Process Development

Table 5. CHX Manufacturing, Filling and Sealing

Unit Operation	Comments
Gel Manufacture	• Disperse and hydrate guar gum with heating in an aqueous solution of sodium acetate trihydrate. • Add in CHX digluconate API solution. • Mix.
Filling/Sealing	• Fills into aluminum foil laminate sachets by automated filling/sealing equipment. • Target fill weight for sachets is 3.3g (range 3.0g–3.6g).

Aid for CTD Module 3.2.P.3.2 – API and CHX Gel Formulation

Table 6. CHX Gel Formulation Composition

Substance	Content
API **(salt forms)**	• dihydrochloride (0.2% aqueous solubility) • diacetate (2% aqueous solubility) • digluconate (highest solubility)
CHX digluconate (7.1%) gel	• 20% w/v aqueous solution (37.81% w/w) • Consists of three excipients (guar gum (1.40 % w/w) as a thickener, sodium acetate trihydrate (0.10 % w/w) as a pH modifier, QS with purified water as a solvent) • 4% w/w equivalent of CHX as the free base • Single-use 3g dose in a foil laminate sachet

Aid for CTD Module 3.2.P.3.3 – Impurity Control Strategy

Table 7. Control of CHX Impurities

CQA Parameter	Specification for control
pH	• Drug product at release is controlled to pH 5.5–6.5.
4CA	• Drug product at release contains <150 ppm.

Aid for CTD Module 3.2.P.3.4 – Analytical and Specifications for CHX Gel

Table 8. Tests and Specifications

CQA Parameter	In-process Specification	Release Specification	Shelf-life specification (acceptance criteria)
Description		A colorless to yellow, translucent gel essentially free from visible particles	A colorless to yellow, translucent gel essentially free from visible particles
Identification of CHX digluconate by: **HPLC** **Ultraviolet**		a. Retention time of CHX peak in the sample solution should be within ± 3% of retention time of CHX in reference solution preparation. b. Ultraviolet maxima of CHX should be within ±3 nm relative to reference standard.	
pH		5.5–6.5	5.5–7.0
Apparent viscosity by viscometer (cPs)		3000–8000 cPs	3000–8000 cPs
Minimum fill	Target: 3.3 g Range: 3.0–3.6 g	As per USP <755> Minimum Fill	
CHX digluconate		6.75–7.45 % w/w	6.39-7.45% w/w

content by HPLC (%w/w)		(95.0%–105.0% of label claim)	(90.0%–105.0% of label claim)
Seal Integrity	Confirm sachet integral (pass/fail)		
Sachet appearance	Confirm satisfactory sachet appearance		

Aid for CTD Module 3.2.P.7 – Manufacturing and Packaging

Table 9. Packaging and Composition

<table>
<tr><th>Unit Operation</th><th>Comments</th></tr>
<tr><td>Sachet Laminate Structure to Conform with European Directive No. 10/2011 for Food Contact and Ph. Eur. 3.3.3 Polyolefins</td><td>
<table>
<tr><th>Outside Layer</th></tr>
<tr><td>Polyethylene terephthalate (12 µm)</td></tr>
<tr><td>Low-density polyethylene white pigmented extrusion laminate</td></tr>
<tr><td>Low-density polyethylene aluminum foil (9 µm)</td></tr>
<tr><td>Low-density polyethylene-extrusion laminate</td></tr>
<tr><td>Low-density polyethylene film (40 µm)</td></tr>
<tr><th>Product Contact Layer</th></tr>
</table>
Example GSK sachet laminate structure
</td></tr>
<tr><td>Extractables/Leachables</td><td>• Undergo a risk assessment: foil laminate material, filling and sealing processing of foil laminate, and gel bulk manufacture.</td></tr>
</table>

References

Web site
usp-pqm.org. Promoting Quality Medicines Technology Transfer Report-Chlorhexidine digluconate (7.1%) gel [May 2019] Available from: https://www.usp-pqm.org/sites/default/files/pqms/article/gsk-chx-gel-tech-transfer-report-6-20-2019.pdf